



## Case Report

# Treatment of Insulin Autoimmune Syndrome - A Tri Prong Approach

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### Abstract

Insulin Autoimmune Syndrome (IAS) manifests as transient self-limiting endogenous hyperinsulinemic hypoglycemia. It is characterized by the presence of insulin autoantibodies which bind insulin and the unpredictable release of insulin from insulin-autoantibody complexes resulting in spontaneous hypoglycemia. It needs to be considered in patients of hypoglycemia (in non-diabetic individuals) to avoid unnecessary investigations and surgical interventions. Treatment of Insulin autoimmune syndrome has always been an enigma. We suggest a tri prong approach, with the pharmacological cocktail of alpha glucose inhibitor, steroids, and diazoxide along with dietary modifications after the elimination of the culprit agent. The targeting of the three major pathogenetic mechanisms when initiated early holds the potential of earlier relief of symptoms and accelerated recovery.

**Keywords:** Hypoglycemia; Insulin autoantibodies; Endogenous hyperinsulinemic hypoglycemia; Insulin Autoimmune Syndrome; Immunomodulators; Alpha-glucosidase inhibitors

**Abbreviations:** IAS: Insulin Autoimmune Syndrome; MAB: Monoclonal Antibody; IAA: Insulin Auto Antibodies; BHOB: Beta-Hydroxybutyrate

### Case Report

54 years aged female, housewife without prior history of diabetes mellitus presented with sudden onset symptoms of sweating, palpitations, tremors, dizziness in early morning hours. These were confirmed to be, due to hypoglycemia by documenting fingerstick glucose values of 42 and 48mg/dl on two different occasions. Her post-meal glucose levels were elevated in the range of 180 mg/dl - 240 mg/dl. Hypoglycemic episodes recurred about 3- 4hrs after a meal. She is hypertensive, and on telmisartan 40 mg, aspirin 75 mg, and atorvastatin 20 mg daily. Recently, she had taken capsules of a multivitamin containing alpha-lipoic acid of 200 mg. She had a history of being positive for ANA, sulpha drug allergy, and contrast allergy-induced anaphylaxis. A critical sample with RBS of 50 mg/dl showed a C-peptide of 17.37 ng/ml, Insulin of 3100 uIU/ml, and Beta-hydroxybutyrate was 0.1 mmol/l.

Given the disproportionately high levels of insulin compared to C-peptide diagnosis of IAS was suspected and titers of insulin antibodies were 236 U/ml. The diagnosis of Insulin Autoimmune Syndrome (IAS) was made and no further evaluation was done.

The supplement containing alpha-lipoic acid was discontinued. She was advised high fiber small frequent meals. Due to the increased frequency and severity of hypoglycaemic episodes, she was initiated on glucocorticoids (Prednisolone 30 mg) and diazoxide 50 mg thrice daily. With persisting episodes of hypoglycemia and postprandial hyperglycemia,  $\alpha$ -glucosidase inhibitor (acarbose) was added to the current regimen after one week, and titrated weekly 150 mg/day. Hypoglycemic episodes were relieved in about 2 weeks of  $\alpha$ -glucosidase inhibitor (acarbose). Steroids were tapered over 3 months, and she remained symptom-free thereafter.

### Introduction

IAS is a rare, self-limiting endogenous hyperinsulinemic hypoglycemia. It is also known as Hirata syndrome named after Yukimasa Hirata, who first reported the case in 1970[1]. It is characterized by spontaneous hypoglycemia, elevated insulin levels, and elevated anti-insulin antibody levels to endogenous

insulin without precursory exposure to the exogenous insulin[2].

The fundamental mechanism of hypoglycemia in IAS is proposed to the presence of large amounts of insulin autoantibodies (IAA). After ingestion of food, there is a rise in blood glucose, followed by an increase in insulin levels. Insulin released binds to IAA blunting its action which results in postprandial hyperglycemia, the latter instigates further insulin secretion initiating the vicious cycle. Insulin-IAA complexes create a reserve of insulin from which unpredictable dissociation of insulin occurs, leading to hypoglycaemia [3].

Hypoglycemia of IAS is therefore dependent on the meal-derived stimulus to beta-cell, their response, and the antibody titre, the latter providing not just the reservoir but also the stimulus for further insulin release. Once incited, the duration of the disorder depends on the half-life of antibodies, their titre, and production.

The perpetuation and magnitude of the disorder depend on the inciting cause, duration, and protracted exposure to the antigen contained in a variety of drugs. Drugs having the Sulfhydryl group act as haptens, and interact with the disulfide bonds of insulin augmenting its immunogenicity. Other causes of endogenous hyperinsulinemia are insulinoma and sulfonyleurea intake, but the level of insulin seen in IAS is never encountered in these aetiologies.

$\alpha$ -lipoic acid is being, increasingly used in the management of neuropathy. It has been associated with the development of insulin autoantibodies, causing hypoglycemia and uncontrolled postprandial hyperglycemia. Especially, when used in patients living with diabetic peripheral neuropathy, it can be a masquerader of worsening glycemic control and variability. A high index of suspicion with detailed drug history is required for a timely diagnosis.

### **Diagnosis**

Diagnosis involves the confirmation of endogenous

hyperinsulinemia which is done by the measurement of insulin and c-peptide during an episode of hypoglycemia. The traditional critical diagnostic criteria are plasma insulin concentrations of  $3\mu\text{U/ml}$  or higher, C-Peptide concentrations of  $0.2\text{ nmol/L}$  or higher, and plasma proinsulin concentrations of  $5.0\text{ pmol/L}$  or higher, while venous blood sugar below  $55\text{mg/dL}$  is the cut-off limit for hypoglycemia in a non-diabetic subject[4]. The presence of insulin autoantibodies of more than  $12\text{ U/L}$  is diagnostic of IAS[5]. Moderately elevated proinsulin and C-peptide concentration, and insulin to C-peptide molar ratio of  $> 1$  are suggestive of IAS[6]. Plasma  $\beta\text{HOB}$  of  $2.7\text{ mmol/L}$  or less suggests hyperinsulinemia with hypoglycemia. The insulin levels are significantly high

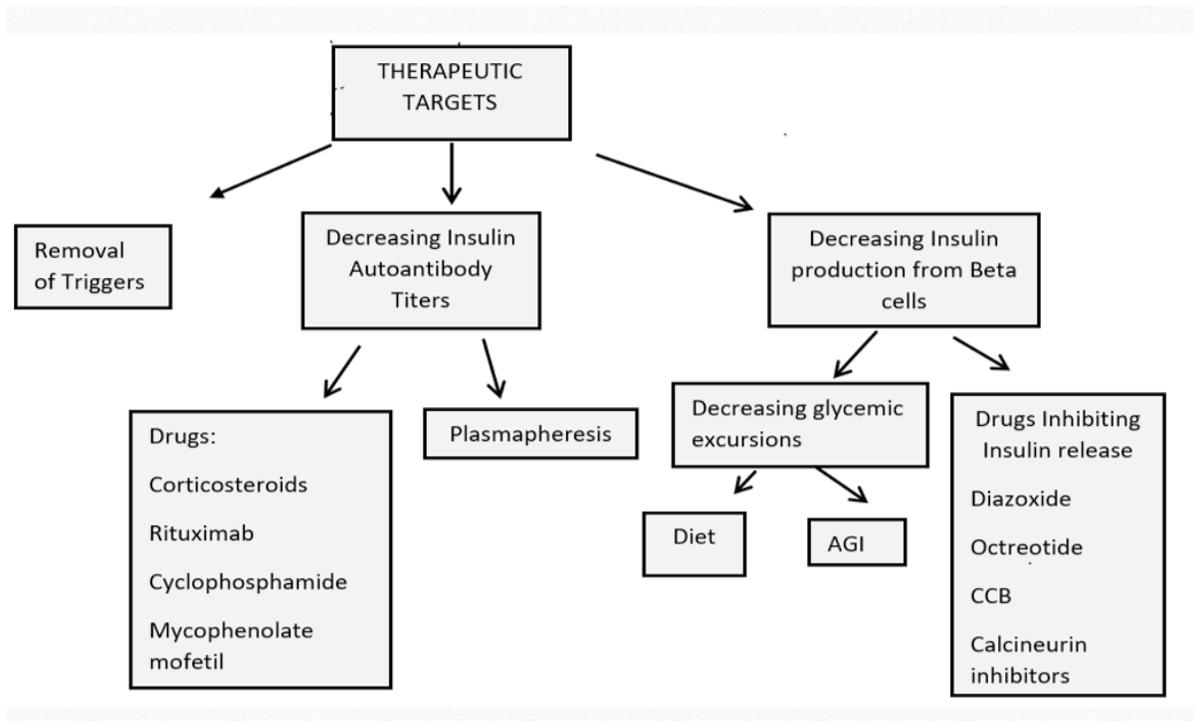
### **Management**

Most cases of IAS are self-limiting, the resolution takes 3-6 months from initial diagnosis [7]. The mechanism of resolution is the waning of antibodies after the inciting cause is addressed, the antibodies may wear off over some time. Cappellini, et al. have demonstrated that in IAS induced by alpha-lipoic acid, the insulin auto-antibody levels decreased after the inciting agent (i.e., alpha-lipoic acid) was withdrawn over 6 months from  $530\text{ U/ml}$  to  $51\text{ U/ml}$ [8].

Presently, there are no guidelines for the management of IAS. The existing approach starts with the trial of dietary modifications. Followed by pharmacological interventions is in those who fail to respond to this.

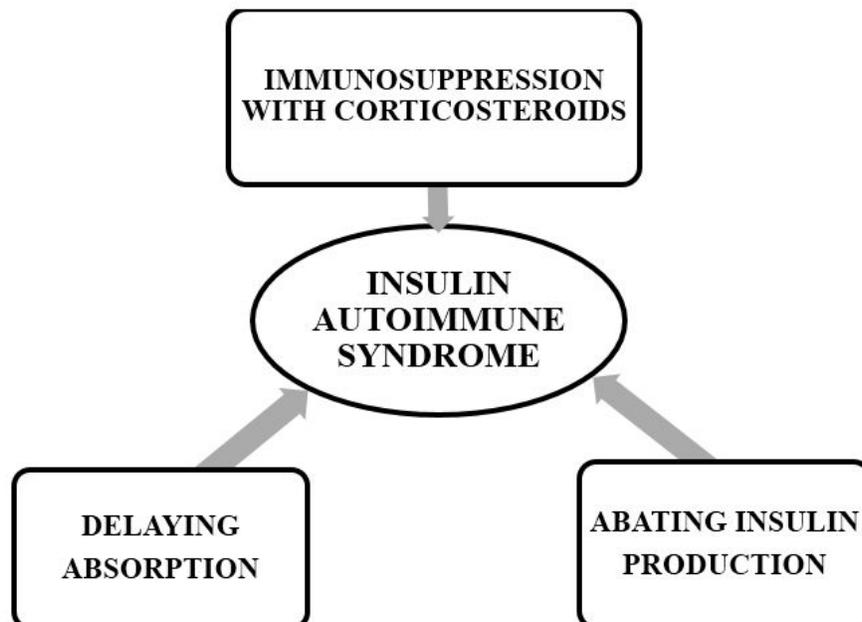
After the withdrawal of inciting drug. The dietary recommendations include eating small frequent meals, avoiding simple carbohydrates, and a high fibre diet. Corn starch has proven beneficial due to delayed absorption and preventing fasting hypoglycaemia [9].

Therapeutic targets in the management of IAS can be categorized as in Figure 1.



**Figure 1:** Therapeutic approach in IAS.

The Tri-prong therapeutic approach alluded to targets the three major pathophysiological mechanisms of the IAS with three different interventions(Figure 2).



**Figure 2:** Pathophysiological targets in IAS management.

### Staggering absorption and blunting glycemc peak

Alpha-glucosidase inhibitors (AGI), acts by inhibiting the membrane-bound intestinal alpha-glucosidase which hydrolyze oligosaccharides, tri-saccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. This intervention staggers the glucose absorption and the post-prandial glycaemic excursions, thus reducing the quantum of insulin synthesis and secretion from the pancreatic  $\beta$  cells. The STARCH study by Joshi SR, et al, showed 67 % of the Indian diet is composed of carbohydrates. Surplus consumption of simple carbohydrates was seen in non-diabetics[10]. The challenges involved in dietary compliance are too well known not just in the Indian context[11].

Glycaemic excursions determine the amount of insulin released from the beta cells, the higher -the excursions, the greater is the insulin secreted and bound to the antibodies for future release. Dietary interventions are directed at addressing this mechanism but given the composition of traditional Indian diets (Starch study) the high glycaemic response to a carbohydrate meal and the poor compliance dietary interventions utilizing alpha-glucosidase inhibitors is practical and viable option. These drugs inhibit the membrane-bound intestinal -glucosidase which hydrolyzes oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine resulting in blunting of glycaemic excursions.

This intervention complements dietary modifications, and especially in those who fail to comply with the new dietary interventions.  $\alpha$ -glucosidase inhibitors (Acarbose) 50 mg once daily to start with, titrated every week to 50 mg thrice daily.  $\alpha$ -glucosidase inhibitors need, slow up-titration for about 3 weeks to minimize the GI intolerance by permitting induction of downstream enzymes. and is done weekly. Early introduction of these agents would permit the delivery of effective dosage early.

### Immunomodulation

Given the central role of antibodies in the causation of this syndrome, immunosuppression therapy is an obvious and attractive option. Corticosteroids besides their immunosuppressive properties also provide substrate for and promote gluconeogenesis. Besides, inhibiting the peripheral uptake of glucose countering hypoglycemia in multiple ways. The usual dosage of prednisolone is 30-60mg and can be tapered and stopped after 2-3 weeks. Other agents include calcineurin inhibitors like Tacrolimus, Rituximab, cyclophosphamide, and Mycophenolate mofetil.

### Decreasing Insulin Production

Diazoxide binds to the SUR1 subunit causing the opening of the intact K-ATP channels, resulting in the blockade of  $\beta$ -cell depolarization with reduced insulin secretion. It is initiated orally at 5 mg/kg/day in three divided doses with a dose that can be gradually increased, if needed, up to a maximum dose of 20 mg/

kg/day. The other agents in this category are octreotide, calcium channel blockers, calcineurin inhibitors.

### Conclusion

IAS is a self-limiting condition causing significant morbidity. Its treatment conventionally includes the identification and withdrawal of the offending agent, dietary modification, and sequential/step-wise addition of immunomodulators, drugs inhibiting insulin secretion, and alpha-glucosidase inhibitor. This approach might delay recovery should the chosen intervention(s) be ineffective. Giving all these drugs together at the very outset constitutes the tri-pronged attack which has the potential of abbreviating this period and providing quicker symptomatic relief while permitting the titration of AGI's to their required effective dose. Although this aggressive approach may not be suitable in all, but necessary in those with repeated distressing hypoglycaemic episodes despite conventional dietary restrictions.

**Declaration of Competing Interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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